IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT Application of
Muller et al.

Group Art Unit: 1618

U.S. App'n Ser. No.: 10/030,417

Examiner: Ebrahim, Nabila G.

Filed: 08/14/2002

Attorney Docket No: 668-59190

For: METHOD FOR CONTROLLED PRODUCTION OF ULTRAFINE MICROPARTICLES AND NANPARTICLES

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28 January 2011

REPLY BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This reply brief is timely filed within two months from the 7 December 2010 mailing date of the Examiner's Answer.

The arguments raised by the Examiner are fully rebutted in Appellant's Appeal Brief and no arguments raised by the Examiner are acquiesced by Appellant.

Appellant provides the following response to the Examiners "Response to Argument" starting on page 6, second paragraph of the Examiner's Answer.

The Examiner erroneously argues that "Desai, the primary reference teaches the reduced or no water dispersion in Example 4" and that "Appellant ignores Example 4 of Desai which teaching 30 mg Taxol is dissolved in 0.55 ml chloroform and 0.05 ml ethanol." See page 6, second paragraph, and page 7, second paragraph in the Examiner's Answer. Example 4 of Desai in fact teaches to use 96% water.

Example 4 of Desai uses 0.55 ml chloroform, 0.05 ml ethanol and 29.4 ml aqueous Tween 80 solution, which Tween 80 solution contains 1 wt.% of Tween 80 and 1 % of chloroform for presaturation, and thus contains consquently 98 wt.% of water. The 98 wt.% of 29.4 ml solution is approximately 28.8 ml of water. Thus, the

30 ml of homogenized mixture of Example 4 of Desai contains 96 % of water. Desai does not at all teach a reduced or no water dispersion in Example 4 as erroneously alleged by the Examiner.

While the Examiner admits that Muller teaches to use a large amount of water, the Examiner argues that Muller does not teach against using less water, "it is noted that nowhere in Muller, the reference teaches that there must be 80% to 99% of water to achieve the reduction of particle size." See page 6, second paragraph in the Examiner's Answer. However, Appellant (who is also the inventor of Muller) submits that Muller teaches that the "dispersion principle is cavitation." See column 4, lines 6-7. Cavitation by definition requires a large amount water and, thus, Muller teaches against using less water. The Examiner's arguments regarding Muller teaching to use the lowest possible surfactant content is irrelevant to the issue of the amount of water actually being used in the process of Muller. Since both Desai and Muller teach to use a large amount of water, the combination of references teaches in a direction away from the low water content used in the claimed invention.

Desai teaches against using a low water content. As discussed in detail in the Brief, Example 7 of Desai shows the influence of organic solvent on the size reducing effect. Already a low content of 4% resulted in an increase of particle size from 150 to 250 nm. Thus, it can be reasonably expected that a further increase of organic solvent content to more than 50%, i.e. by a factor of more than 10, will further and dramatically decrease the size reducing effect of the homognizer so that particles are expected to be produced having a size far beyond the presently claimed limit.

The Examiner continues to confuse use of the already made particles in a non-aqueous dispersion medium (Abstract and claim 29 of Muller) with using a non-aqueous dispersion medium to produce the particles (claimed invention). The Examiner argues that "Appellant's assertion also ignores Muller '410 which teaches in the (abstract and claim 29) the possibility of using non-aqueous medium for the dispersion." See page 9, first paragraph in the Examiner's Answer. The Examiner has ignored Appellant's argument in the Brief. As stated in the Brief, Appellant respectfully submits that the Examiner misinterprets the Abstract of Muller, that "a step of further modifying a particle can still be considered as a method of producing

a particle." The Abstract of Muller merely discloses that the already produced drug carrier comprises particles of a pure active compound, which is insoluble or sparingly soluble in organic solvents. Claim 29 of Muller recites that the already produced particles can be dispersed in a non-aqueous dispersion medium. This language absolutely does not teach or suggest that organic solvents, which contain less than 50 wt.% water, should be used as a dispersion medium in a piston-gap homogenizer to produce the particles. The Absract and claim 29 only teach dispersing particles already produced by the water-based high pressure homogenization process of Muller in an organic solvent for further purposes, which cannot be read as a production of such particles in an organic solvent dispersion medium. The Examiner makes a similarly erroneous argument in the first paragraph on page 12 of the Examiner's Answer. The abstract of Muller does not teach to use 0% water when making the particles, only when dispersing the already formed particles for use as a carrier.

The Examiner's inherency argument in the third paragraph on page 12 of the Examiner's Answer is based on the erroneous conclusions that Example 4 of Desai teaches to a low amount of water and the abstract of Muller teaches to use 0% water. Thus, the claim term "without cavitation" is not an inherent property of Desai and Muller.

The Examiner admits that Desai and Muller do not disclose using a temperature under freezing, and that the combination of references teaches using a "reduced content of water" during the homogenization. See the fourth paragraph on page 12 of the Examiner's Answer. Since the combination of references does not teach or even suggest using a "reduced water content" nor the use of freezing temperatures, the Examiner has not made a prima facie case of obviousness.

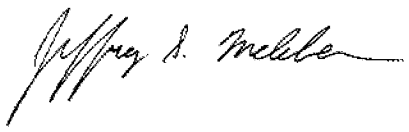
The Examiner argues that that "since the prior art teaches the same dispersion and homogenizer, the same result thereof would be expected to occur." See page 9, last paragraph in the Examiner's Answer. However, as discussed above, the combination of references does not teach or suggest using a reduced water content and, thus, the combination does not teach the same dispersion and result as the claimed invention.

The Examiner argues that "it is clear that shear and impact forces are alternatives to cavitation" and, thus, the different homogenizers are equivalent and the unexpected results of record can be ignored. See pages 10-11 in the Examiner's Answer. Appellant submits that the teachings of Muller (Appellant is the inventor of Muller) with respect to cavitation and shear forces have to be divided. The cavitation effect is related to the use of a piston-gap homogenizer, while the shear and impact forces are related to other devices such a microfluidizer or nanojet using the jet stream principle. See column 4, lines 16-21, and column 5, lines 6-7, respectively. Since the claimed method requires the use of a piston-gap homogenizer, the mention of shear and impact forces related to other devices in Muller are of no relevance. Even if the shear and impact forces are relevant, and they are not, such forces do not support the Examiner's dismissal of the unexpected results of record relating to the claimed piston-gap homogenizer.

Conclusion

In view of the lack of *prima facie* cases of obviousness, the many differences between the claimed invention and the cited references, and the unexpected advantages of the claimed invention, it is believed that this application clearly and patentably distinguishes over the combination of the cited references and is in proper condition for allowance. Accordingly, Appellants respectfully request that the Board allow claims 1-17, 20, 24-29, 31-34 and 38-47 over the cited reference.

Respectfully submitted,
Manelli Denison & Selter, PLLC



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